Russel A. Bantham
GENERAL COUNSEL
AND
SENIOR VICE PRESIDENT

PhRMA

December 14, 1999

Dockets Management Branch
Food and Drug Administration
Room I-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Response of Pharmaceutical Research and Manufacturers of America (PhRMA) to the Citizen Petition of the National Association of Pharmaceutical Manufacturers (NAPM) on Criteria for Approval of Generic Versions of Pioneer New Drugs – Docket No. 99P-1658 CP1

In accordance with 21 C.F.R. 10.30(d), the Pharmaceutical Research and Manufacturers of America (PhRMA) submits these comments in opposition to the above-referenced citizen petition submitted by the National Association of Pharmaceutical Manufacturers (NAPM) requesting the Food and Drug Administration (FDA) to amend the criteria for determining that a generic version of a pioneer drug is "the same" and thus may be approved under the requirements of Section 505(j)(2)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to research on medicines that allow patients to lead longer, healthier, and more productive lives.

PhRMA opposes the NAPM petition for the following reasons. First, the proposed amendments contradict the express language of the statute. Second, the proposed amendments violate the basic policy established by Congress in the Drug

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Price Competition and Patent Term Restoration Act of 1984. Third, it is inappropriate to attempt to revise longstanding statutory and agency policy on the basis of a single fact-dependent court decision. Fourth, the criteria suggested in the NAPM petition are incomplete and fail to provide adequate substantive guidance with respect to future action.

1. The Proposed Amendments are Inconsistent With the Statutory Language.

Section 505(j)(2)(A)(ii) of the FD&C Act requires an abbreviated NDA to show that the active ingredient is "the same" as that of the pioneer drug. The contemporaneous and long-standing FDA interpretation of this requirement, as well as the clear congressional intent, is that the active ingredient in the generic version must be "identical" to the active ingredient in the pioneer drug. 21 C.F.R. 314.92(a)(l) and 320.1(c); H.R. Rep. No. 98-857, Part 1, 98th Cong., 2d Sess. 21 (1984). Section 505(j)(2)(C) of the FD&C Act provides that, where the generic drug is not the same as (identical to) the pioneer drug, the generic manufacturer must obtain FDA approval of a "suitability" petition before submitting an abbreviated NDA. FDA has made clear in 21 C.F.R. 314.93(a) and (b) that a suitability petition can only cure a difference in an inactive ingredient, not the active ingredient, in a single active ingredient drug product.

Sections 505(j)(2)(A)(ii) and 505(j)(3)(C)(i) of the FD&C act place the burden on the abbreviated NDA applicant to provide information to show that the active ingredient in the generic version of a new drug is in fact the same as (identical to) the

active ingredient in the pioneer drug. Under the regulatory amendments proposed by NAPM, this burden of proof would, in effect, be shifted to FDA to act as a surrogate in providing such information, or to the manufacturer of the pioneer drug to demonstrate that a similar (but not identical) active ingredient is not the same as the pioneer active ingredient. This would violate both the statute and the congressional policy on which it is based

An active ingredient that is not the same as (identical to) the pioneer drug active ingredient is no different under the FD&C Act than any other new chemical entity (NCE). All NCEs require an appropriate data package of nonclinical and clinical testing to demonstrate safety and effectiveness.

If the active ingredient in the pioneer new drug were manipulated by the NDA holder so that it was no longer the same as (identical to) the version that FDA approved in the original NDA, the relevant FDA Office of Drug Evaluation would uniformly require an adequate data package on safety and effectiveness before approving that new version. The same rule must apply to new generic versions of pioneer active ingredients. The FD&C Act does not establish or permit different rules for altering active ingredients as between the pioneer manufacturer and generic companies.

The statute is clear on its face, and the existing FDA regulations accurately reflect the congressional policy as it was developed in 1984. No changes in these regulations is justified or needed.

2. **The Proposed Amendments are Inconsistent With Congressional Policy as Reflected in the FD&C Act.**

Congress required that the generic version of a new drug be shown by the abbreviated NDA applicant to be the same as (identical to) the pioneer drug in order to obtain an abbreviated NDA. Congress could have chosen different language. It could, for example, have borrowed the then-existing FDA phrase of "identical, similar, or related" that FDA established for the coverage of NDAs under the drug efficacy study implementation (DESI) program in the late 1960s. Instead, Congress declined to set such a broad and nonspecific standard. It chose, instead, to require that the applicant demonstrate that the generic version is the same as (identical to) the pioneer version. Drugs that were merely similar or related were excluded from the abbreviated NDA process. The NAPM petition now seeks to overrule that congressional determination by establishing a "not-quite-the-same" category of generic drugs that are similar or related to the pioneer drug but are not the same, and yet nonetheless would qualify for an abbreviated NDA. This would permit the generic drug industry -- and by logical extension, fhe pioneer drug industry as well -- to obtain approval for drugs that are essentially new drugs, without the nonclinical and clinical investigations necessary to protect the public health because the approvals would be based on studies conducted for a pioneer drug that is not the same as the generic version. Since the generic drug is not the same as the pioneer drug, it may not have the same benefits and side effects. A generic company would thus be empowered to take a pioneer drug, modify it, and

market it as a generic version without undertaking the clinical investigations required for a new drug. The net effect is to require the pioneer manufacturer to establish the significance of any differences between the generic drug and the pioneer drug -- a result clearly not contemplated by the statute. This would violate the unambiguous congressional policy established in the 1984 Act, by expanding the very narrow exemption created for abbreviated NDAs to a much broader universe of drugs.

This policy, as reflected in the FD&C Act drug approval provisions, is designed to assure that adequate and well controlled effectiveness studies and adequate safety studies have been performed on every marketed drug. For innovator products, this goal is achieved by requiring such studies in the NDA. For abbreviated NDAs, the burden is placed on the generic manufacturer to demonstrate that its product has the same active ingredient as has been shown by the innovator's testing to be safe and effective. The NAPM proposal would remove this protection of the public by permitting the introduction of a new class of drugs that, though similar to products shown to be safe and effective, have themselves never been subjected to the type of testing that is the statutory standard for marketing of drugs in this country.

3. There is No Reason to Consider Any Change in the Regulations.

The NAPM petition cites only a single court decision, Serono Laboratories, Inc. v. Shalala, 158 F.3d 1313 (D.C. Cir. 1998), in support of its position.

Like all court decisions of this type, Serono is completely fact-specific. It did not invalidate the current FDA regulations. Rather, the court upheld FDA's action as satisfying those regulations. Nor does the decision set forth new criteria or purport to establish broad policy. Accordingly, the Serono decision, which still awaits trial on the merits, provides no basis for changing those regulations.

4. **The NAPM Petition Proposes Incomplete and Nonspecific Criteria That Are Not Helpful in Developing Appropriate FDA Policy.**

The NAPM petition establishes no substantive criteria for determining when an abbreviated NDA will be appropriate for a generic version of a drug that is not the same as (identical to) the pioneer drug. Rather, the NAPM proposes simply that FDA make a 'case by case determination," i.e., that the agency do whatever it wishes to do under the circumstances, without the benefit of clear and understandable criteria. This would, in itself, represent **a** violation of law, as was recently held in Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999).

PhRMA believes that nonclinical and clinical trials are essential to determine that a generic version of an active ingredient in a pioneer drug that is not the same as (identical to) the pioneer is in fact safe and effective, as required by the FD&C Act. This is true regardless whether the generic version is the subject of an application under Section 505(b)(2) or Section 505(j) of the FD&C Act. The very Institute of Medicine report that is appended to the NAPM petition points out that two therapeutic

substances that are not the same (identical) can in fact lead to significant differences. The NAPM petition itself establishes that experts disagree on the criteria that should govern when two different molecules are likely to have different effects. Until these issues are resolved, any showing less than that the generic version is the same as (identical to) the pioneer drug should result in a determination that nonclinical and clinical trials are required.

5. The NAPM Proposal Does Not Provide a Procedure for FDA to Decide Whether a Nonidentical Generic Drug is Close Enough to the Pioneer Drug to be Considered the Same

If FDA interprets and applies the FD&C Act as written, it will in almost all cases be self-evident whether the generic product has the same active ingredient as the pioneer. If FDA ignores the statute's mandate and begins to make "case-by-case" decisions that variations of active ingredients are "close enough," however, it will be necessary to establish a fair and rational process for decisionmaking on the issue of whether two active ingredients that are not identical are nonetheless close enough to be the same. It would be essential in that case that FDA recognize that the burden is on the generic applicant to establish that there is no significant difference between the two active ingredients and that a meaningful opportunity must be provided -- before FDA makes its decision -- for the affected public, and particularly the innovator manufacturer which is usually the party that is most knowledgeable about the drug, to provide input on the question. Because PhRMA believes that the NAPM petition should

simply be denied, it will not address the procedural issues further here. If, however, FDA should decide to entertain the NAPM proposal, it should seek public input on the appropriate administrative procedures to be utilized.

6. Conclusion.

PhRMA urges FDA to deny the NAPM petition and to retain the current regulations governing abbreviated NDAs unchanged.

Russell A. Bantham
Senior Vice President & General Counsel
PhRMA